REMARKS/ARGUMENTS

Claims 1, 3, 5-7, 13-27 are pending in the application and presented for examination. Claims 1, 25 and 27 have been amended. Claims 4, 8, 10 and 11-12 have been canceled without prejudice or disclaimer. No new matter has been entered with the foregoing amendments. Reconsideration is respectfully requested.

I. FORMALITIES

Independent claims 1, 25 and 27 have been amended to recite that the core tablet comprises a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose. Support for these features are found, for example, in claim 4. Consequently, claim 4 has been canceled without prejudice.

In addition, claims 1, 25 and 27 have been amended to recite that the outer layer is made from a hydrogel-forming polymer substance and a hydrophilic base, wherein the hydrogel-forming polymer substance is made from at least one type of polyethylene oxide, and the hydrophilic base is polyethylene glycol. Support for these amendments are found, for example, in claims 8 and 12. Consequently, claims 8 and 12 have been canceled without prejudice. In view of the foregoing support, no new matter has been entered with the foregoing amendments. Accordingly, Applicants respectfully request that they amendments be entered.

II. REJECTION UNDER 35 U.S.C §102(b)

The Examiner has maintained the rejection of claims 1, 3, 4, 7, 8, 11, 12, 14-19, 24 and 27 under 35 U.S.C. § 102(b) as allegedly being anticipated by U.S. Patent No. 5,922,352 ("Chen *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Chen *et al.* teach a tablet having a delayed-release core and an outer extended-release coating that provides bioequivalent pharmacokinetic performance (*i.e.*, *maintains* a sustained 24 hour drug plasma level) for a calcium channel blocker (see, column 2, lines 45-52).

Both the core and the coating contain the calcium channel blocker drug. According to Chen *et al.*, the core of the controlled-release tablet contains a micronized crystalline calcium channel blocker. The micronized crystalline calcium channel blocker such as nifedipine is combined with an ***enteric coating agent*** which may contain a suitable plasticizer and a solid pharmaceutical acceptable filler or solid diluent. Preferably, micronized nifedipine will have a surface area of 5 m^2/g or higher (see, column 2, lines 58-68.)

The enteric polymers that are taught by Chen *et al.* are set forth at the bottom of column 2, bridging to column 3, reproduced here for the Examiner's convenience:

> The enteric polymers which may be used include Eudragit S (methacrylic acid/methyl methacrylate copolymer with a 1:2 ratio of MA to MMA) or Eudragit L (methacrylic acid/methyl methacrylate copolymer with a 1:1 ratio of MA to MMA), hydroxypropylmethylcellulose phthalate (HPMCP), cellulose acetate phthalate, shellac etc. A granulation is formed of the enteric coated calcium channel blocker compound and this granulation is compressed into a tablet which is used as the delayed releasing core of the tablet of the invention. The granules which form the compressed core may contain a pharmaceutically acceptable diluent in addition to the calcium channel blocker compound.

As such, Chen *et al.* relate to a tablet having a delayed release core, wherein the core has an enteric material. Thus, the tablet according to the teaching of Chen *et al.* is affected by a change in pH. For example, under the "Summary of the Invention," as well as claim 1, Chen *et al.* clearly disclose a core including "(i) particles of a calcium channel blocker compound ***coated with an enteric polymer*** that are dispersed onto a solid pharmaceutical filler." [Emphasis added]. In order to achieve controlled-release or delayed-release of the calcium channel blocker in the colon, the enteric polymer "protects" the active ingredient in the low pH environment of the stomach.

At column 3, lines 22-30, Chen *et al.* further teach an external layer having the same drug as the drug core:

> The core of the tabletted dosage form of the invention is provided with an external layer of an extended release formulation *which also contains the calcium channel blocker compound*. The external coat is formed by compressing the granules around the delayed release core to form an extended release external layer. The external coat of the extended release formulation will contain effective amounts of a pharmaceutically acceptable polymer which forms a hydrogel as well as tablet lubricants.

In the teaching of Chen *et al.*, the core and the external layer both contain a drug.

Under MPEP § 2131:

> [a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987).

Unlike the teaching of Chen *et al.*, the current invention is drawn to a time-release tablet, having two distinct layers each comprising a different formulation. The two distinct layers of the inventive formulation are as follows:

1) a core tablet that has a drug and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose, wherein the core tablet erodes approximately 40% to approximately 90% in the digestive tract of the subject; and

2) an outer layer wherein the outer layer is made from at least one type of polyethylene oxide, and polyethylene glycol and does not contain the drug.

The core-tablet layer of the of the multi-layered time-release inventive formulation does contain a drug, however, the outer layer of the inventive tablet does not contain a drug. In addition, unlike Chen *et al., the core of the inventive tablet does not contain enteric polymers.*

Moreover, unlike the delayed enteric coated core of Chen *et al.*, the inventive timed-release tablet means that after a specific lag time, the drug from the pharmaceutical

preparation is released. In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. As such, all the limitation of the claims are not found in Chen *et al.* and thus, the claims are not anticipated.

Further, Applicants respectfully traverse the Examiner's characterization of the claim as "a product-by-process" claim. As set forth in the M.P.E.P § 2173.05(p), a product-by-process claim is a product claim that defines the claimed product in terms of the process by which it is made. The instant claim recites:

> ...*wherein said core tablet erodes approximately 40% to* approximately *90% in the digestive tract of said subject, wherein said core tablet does not contain a hydrogel-forming polymer.*

The foregoing characterization is a feature of the claimed product. It is **not** how the product is made. Accordingly, Applicants respectfully request that the Examiner withdraw the rejection.

III. FIRST REJECTION UNDER 35 U.S.C §103(a)

The Examiner has maintained the rejection of claims 5, 6, 10, 13, 21, 22, 23 and 25 under 35 U.S.C. § 103(a) as allegedly being obvious over Chen *et al.,* in view of EP 0 661 045 A1 ("Sako *et al.*"). to the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

As set forth in M.P.E.P. § 2143:

> [t]o establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in the applicant's disclosure.
>
> I*n re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)

All three elements set forth above must be present in order to establish a *prima facie* case of obviousness. Applicants assert that a *prima facie* case of obviousness has not been established for the following reasons: 1) there is no suggestion or motivation to modify the references; 2) there is no reasonable expectation of success; and 3) the cited art references do not teach or suggest all the claim limitations.

1. There is no Suggestion or Motivation to Modify the References

Applicants state that there is simply no motivation or suggestion provided in the cited references to modify their teaching in the way the Office Action has contemplated. Obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching, suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. *In re Fine*, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones*, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992).

The present invention relates to a timed-release compression-coated formulation. Timed-release means, for example, that after a specific lag time, the drug from the pharmaceutical preparation is released (see, Figure 1 of the specification). In the present invention, timed-release is achieved by the specific formulation of the core tablet and outer layer. The core tablet comprises the active ingredient and a freely erodible filler, wherein the freely erodible filler is 1 or 2 or more selected from the group consisting of malic acid, citric acid, tartaric acid, polyethylene glycol, sucrose, and lactulose, and an outer layer wherein the outer layer is made from at least one type of polyethylene oxide, and polyethylene glycol and does not contain a drug.

Importantly, the core tablet is capable of approximately 40 to approximately 90% erosion. Surprisingly, Applicants have found that a percent erosion of the core tablet of approximately 40 to approximately 90% is necessary for an ideal timed-release pharmaceutical preparation having high bioavailability (see, page 4, lines 16-24 of the specification). Before the

advent of the present invention, the requirement for 40 to approximately 90% erosion to obtain an ideal timed-release pharmaceutical preparation was unknown.

Chen *et al.* clearly disclose a core including "(i) particles of a calcium channel blocker compound ***coated with an enteric polymer*** that are dispersed onto a solid pharmaceutical filler." An enteric polymer is a feature of controlled-release. Chen *et al.* teach a tablet having a delayed-release core and an outer extended-release coating that provides bioequivalent pharmacokinetic performance (i.e., *maintains* a sustained 24 hour drug plasma level) for a calcium channel blocker. Both the core and the coating contain the calcium channel blocker drug. As such, there is simply no teaching or suggestion to modify the controlled-release features of Chen *et al.* to make it a timed-release formulation as is currently taught and claimed.

Sako *et al.* do not supply the deficiencies of the primary reference. Sako *et al.* teach a sustained-release tablet in a single-layered formulation. Sako *et al.* teach a tablet that contains a *single-layer*, *i.e.*, a homogeneous formulation which comprises a i) a drug, ii) an additive providing for the penetration of water in to the core of the preparation, and iii) a hydrogel-forming polymer. Thus, the teachings of Chen *et al.* and Sako *et al.* cannot be combined easily, and even if they are combined, it is hardly possible to achieve the current invention.

As set forth in the present claims, the core tablet in the inventive formulation ***does not*** contain a hydrogel polymer. This is in clear contrast to the invention to Sako *et al.*, which is for a homogenous tablet comprising i) an active agent; ii) an additive, *e.g.*, a hydrophilic base; ***and iii) a hydrogel forming polymer***. As there is simply no teaching or suggestion to arrive at the claimed invention in view of the combination of references, the present invention is not rendered obvious.

Chen *et al.* and Sako *et al.* either alone or when combined, simply do not teach or suggest the specific combination of a core comprising the freely erodible filler for a drug that is 1 or 2 or more selected from the group consisting of malic acid, citric acid and tartaric acid, polyethylene glycol, sucrose, and lactulose, and the outer layer that is made from at least one type of polyethylene oxide, and polyethylene glycol. As there is simply no teaching or suggestion to arrive at the claimed invention in view of the combination of references, the

present invention is not rendered obvious. Accordingly, Applicants respectfully request that the rejection of the claims be withdrawn.

2. There is No Reasonable Expectation of Success

In addition, there is no reasonable expectation of success that the modification that the Office Action contemplates will succeed. "Both the suggestion and the expectation of success must be found in the prior art, not the Applicants' disclosure." *In re Dow Chem. Co.*, 5 USPQ2d 1529, 1532 (Fed. Cir. 1988).

Chen *et al.* clearly disclose a core including "(i) particles of a calcium channel blocker compound coated with an enteric polymer that are dispersed onto a solid pharmaceutical filler." An enteric polymer is a feature of controlled-release. Further, Chen *et al.* teach that the core and the external layer both contain a drug.

Sako *et al.* teach a sustained-release tablet in a *single-layered* formulation. A skilled artisan would have no reasonable expectation of success in view of the combination of these references to arrive at the claimed invention of a timed-release formulation in a multi-layered composition comprising a core tablet and an outer layer, in which the core tablet does not contain a hydrogel polymer.

As set forth in the present claims, the core contains the drug, but ***does not*** contain a hydrogel polymer. Further, the outer layer ***does not*** contain the drug. A skilled person would have no expectation of success of a preparing an efficacious multilayered tablet as presently claimed in view of the cited references. That is, a multi-layered composition comprising a core tablet and an outer layer wherein the core contains the drug, but ***does not*** contain a hydrogel polymer, and the outer layer ***does not*** contain the drug. As such, Applicants respectfully request that the Examiner withdraw the rejection.

3. The Cited Art References Do Not Teach All Limitations of the Claims

The prior art references must teach or suggest all the limitations of the claims. *In re Wilson*, 165 USPQ 494, 496 (C.C.P.A. 1970). Applicants assert that the prior art references

do not teach or suggest all the limitations of the claims and therefore, the obviousness rejection is untenable.

The combination of the references does not teach all the limitation of the claims. Neither reference teach a multi-layered tablet, wherein the core contains a drug, but ***does not*** contain a hydrogel polymer, and the outer layer does not contain the drug. These features are not taught or even suggested in the cited references.

As such, Applicants respectfully request that the Examiner withdraw the rejection.

IV. SECOND REJECTION UNDER 35 U.S.C §103(a)

The Examiner has maintained the rejection of claims 20 and 26 under 35 U.S.C. § 103(a) as allegedly being obvious over Chen *et al.* in view of EP 0 709 386 A1 ("Taniguchi *et al.*"). To the extent the rejection is applicable to the amended set of claims, Applicants respectfully traverse the rejection.

Applicants respectfully assert that the dependent claims 20 and 26, are not obvious over the combined disclosures of Chen *et al.* and Taniguchi *et al.* because the independent claims, *e.g.*, claims 1 and 25 are not obvious over the cited disclosures. In particular, Applicants respectfully assert that the cited references do not teach or suggest Applicants' claimed feature of a timed-release formulation in a multi-layered composition comprising a core tablet and an outer layer, wherein only the core contains a drug.

Chen *et al.* teach that the core and the external layer both contain a drug. Taniguchi *et al.* teach benzazepeine compounds and pharmaceutical compositions thereof. Taniguchi *et al.* disclose a list of general pharmaceutical ingredients that can used to formulate a tablet composition comprising the benzazepeine compounds (*see*, page 27, lines 30-37). However, Applicants assert that there is no teaching or suggestion in Taniguchi *et al.* for a multi-layered timed-release tablet having a core tablet that does not contain a hydrogel polymer. The combination of the references does not teach all the limitation of the claims. Neither reference alone or in combination teach a multi-layered tablet, wherein the core contains a drug, but ***does not*** contain a hydrogel polymer, and the outer layer does not contain the drug.

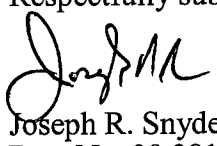
In view of the above, Applicants respectfully assert that the combined disclosures of Chen *et al.* and Taniguchi *et al.* do not teach or suggest all the limitations of the claimed invention. As such, Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 925-472-5000.

Respectfully submitted,



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